REMARKS

Claims 1-6 have been examined, claims 2, 3, and 6 are amended, and claim 7 -11 are added herein. Accordingly, claims 1-11 are now pending in the application. Reconsideration of all outstanding objections and rejections and reexamination is requested.

The disclosure is objected to because it contains an embedded hyperlink and because it contains a blank space for the provisional application number. The specification has been amended to remove the embedded hyperlink and to include the application number of the provisional application.

Claims 4, 5, and 6 are rejected under 35 U.S.C. §112 as being indefinite. Those claims have been amended to conform to the examiner's suggestions.

The claims have been rejected under 35 U.S.C. §103(a) as being unpatentable over Heppelmann et al. in view of Cole et al. and Emmert-Buck et al.

The present invention, as recited for example in claim 1, recites the step of rasterizing a set of tissue samples into a multidimensional spatial grid of indexed tissue sub-samples of a biological sample, with indices of an indexed tissue sample indicating the location of the indexed tissue sample in the multidimensional spatial grid. Analysis is performed on each sub-sample to determine one or more quantitative measures of biological activity These indexes are then utilized to link the biological activity data characterizing each indexed tissue sub-sample to a multidimensional morphological spatial matrix of image data based on the biological sample.

As described in the specification, the rasterization process includes physically sampling the biological sample in a regular raster array, so that tissue samples are taken in a regular multidimensional matrix pattern across each of the spatial dimensions of the biological specimen. Application at page 6, lines 28-30, page 7, line 33 to page 8 line 10, and Fig. 2.

Thus, tissue rasterization step of claim 1 which yields the morphological spatial matrix, samples the tissue in a regular raster array pattern, without regard to the underlying morphological details, and therefore creates an "image" of the biological activity which is overlaid on whatever the underlying morphology is, thereby creating a secondary volumetric image of the tissue itself.

The claimed method is a "survey" approach to characterizing the tissue since the entire volume of the tissue is sampled and rasterized without regard to the underlying morphology.

Hepplemann shows a serial-sectioning histology technique that uses alternating serial histological sections of a biological sample. The first set of histological samples is examined under

a light microscope to examine gross structures down to a few micrometers. Heppelmann et al., page 163, last paragraph. If further examination of a specific area at higher resolution is desired, a corresponding sample from the alternating set of samples is re-embedded for examination utilizing transmission electron microscopy (TEM). Id. at page 164. Thus, Hepplemann teaches using the second interleaved set of sections for performing one or more specifically-targeted re-embeddings for creation of ultra-thin sections for electron microscopy viewing.

Hepplemann also teaches computer-aided contour reconstruction of a nerve bundle using best- fit alignment after the outlines of interesting structures have been digitized. Outlines of structures are plotted while shading and contours were drawn by hand. Id. at page 169-170, Fig. 4.

The Cole reference is discussed in the background section (first para of the 3D localization section) of the patent specification. Similar to Hepplemann, no tissue rasterization is done by Cole. Cole just selects specific cell groups from specific cross section images, and then uses laser microdissection to excise those specific cell groups for microarray analysis. The rest of the tissue is then stained for visual imaging, thereby rendering the rest of the tissue unavailable for microarray analysis.

The Farr reference merely shows that one can study specific cells for a set of several biological parameters at once and includes graphs depicting the relative concentration of specific chemical as a function of various concentrations of another chemical.

The Emmert-Buck reference is also discussed in the background section of the specification. Emmert-Buck shows only that laser-capture microdissection can be used to excise a specific area from a tissue section mounted on a microscope slide.

The examiner states that Heppelmann describes performing these three dimensional reconstructions with graphical techniques and computer-aided methods featuring a spatial matrix of image data as seen in Fig. 4. It is further stated that it would have been obvious to utilize improved methods of comparison of multidimensional graphic data expression representation to microscopy data, as stated in Cole, via three-dimensional histological techniques to increase understanding of complex morphological structures as stated my Heppelmann and using simple and precision tissue extraction with laser capture microdissection that minimizes contamination, as stated by Emmert-Buck, and displaying the gene expression data in easy-to-read-three-dimensional graphs as shown by Farr because these exact and efficient techniques would improve accuracy and visual representation

for easy interpretation of correlations between the two types of data available to scientists at the time of the invention.

This rejection is respectfully traversed for the following reasons. As set forth above, there is no suggestion or teaching in any of the references of the claimed step of rasterizing tissue from said first biological tissue sample into a multidimensional spatial grid of indexed tissue sub-samples, with indices of an indexed tissue sub-sample indicating the location of the indexed tissue sub-sample in the multidimensional spatial grid.

The reference Hepplemen discloses re-embedding corresponding samples of structures examined by the light microscope. There is no disclosure of the rasterization of the tissue sample into a regular array of sub-samples. The computer-aided imaging step of Hepplement is used to draw outlines of the structures of interest.

Thus, Hepplemann traces structures in a CAD-like wireframe-modeling system, which results in a set of contour polygons. The "spatial matrix of image data" in figure 4, which the examiner refers to, is not a pixel-basd or voxel-based image as required by claim 1, but rather it is a set of consecutive contour shapes. Hepplemann, therefore, is interested only in the external shapes of the nerves they are trying to study, and their various topological relationships, not in volumetric imaging of the tissue itself.

Similar to the Hepplemann reference, the hypothesis-driven Cole approach is the antithesis of the survey-based approach set forth in the claim. Since Cole is following an a priori idea of what is important, and is therefore studying only those areas, Cole never teaches or even suggests that one should perform the microanalysis across a set of regularly arrayed locations across the tissue, which is the approach that claim 1 teaches.

Turning next to the Emmert-Buck reference, nowhere does this reference advocate or even suggest that the technique should be used to systematically excise a set of areas in a regular raster array, as described by the applicants. In fact, it teaches away from that by teaching that one should use laser microdissection to carefully excise around the contours of specific cells, rather than lasing a regular grid pattern across the section as described in the patent application.

Finally, with regard Farr, the graphs of Farr do not in any way correlate the data spatially to the sample.

Thus, none of the cited references disclose or suggest the recited claim steps and thus there is no teaching that would make the claimed combination obvious. The examiner has used the

presently claimed invention as a guideline to combine various elements from the references and supply missing elements not shown in any of the references. However, at the time the application was filed no such guideline was available to persons of skill in the art. A general recognition that improved visualization techniques are beneficial without specific teachings of the elements of the claimed combination does not make a claim obvious.

Further, as described above, none of references are directed to solving the same problem as the claimed method and are therefore less likely to make the claim obvious.

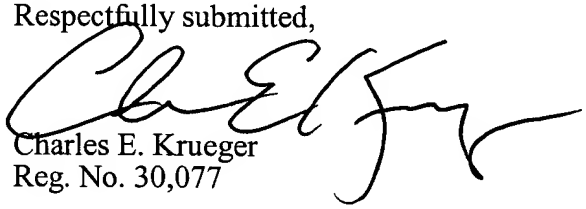
Claims 2-11 also include the rasterization limitation and are thus allowable for the same reasons as claim 1.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (925) 944-3320.

Respectfully submitted,



Charles E. Krueger
Reg. No. 30,077

LAW OFFICE OF CHARLES E. KRUEGER
P.O.Box 5607
Walnut Creek, CA 94596
Tel: (925) 944-3320 / Fax: (925) 944-3363